Relation of Portal Hemodynamics to Cardiac Output During Mechanical Ventilation with PEEP

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The relation of portal hemodynamics to cardiac output (CO) during mechanical ventilation with 15 cm H_2O PEEP was studied in 12 dogs under pentobarbital anesthesia. Cardiac output was measured by thermal dilution. Portal vein flow (PF) and superior mesenteric artery flow (SMAF) were measured by electromagnetic flow probes. Intraesophageal, intraabdominal, portal vein (PVP) and intrathoracic caval (CVP) pressures, as well as the intraluminal venous pressure gradient across the liver (PVP-CVP) were measured. Intravascular volume was expanded with dextran prior to the addition of PEEP. In nine animals, dextran plus PEEP maintained CO and visceral flows within 3% of control. In three animals, CO and visceral flows fell to the same proportion. There was no increase in hepatic resistance. PF showed a linear correlation with SMAF, and SMAF had a linear correlation with CO. In these experiments, the effect of PEEP on portal hemodynamics system is primarily the consequence of reduced CO.

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EXPERIMENTAL OBSERVATIONS during mechanical ventilation with PEEP have noted a reduction in hepatic artery and portal vein flow concomitant with an apparent increase in portal venous pressure. Some observers have concluded from these observations that PEEP redistributes cardiac output[1] and increases hepatic resistance to portal flow.[2] In contrast, our own previous experimental studies of portal hemodynamics have suggested that the effects of PEEP result, primarily, from reduced cardiac output.[3] In previous experiments,[1-4] however, it has been difficult to separate the direct effects of PEEP from those caused secondarily by the reduction in cardiac output. The distinction is an important one clinically. If portal changes are secondary to changes in cardiac output, preventative or corrective measures can be implemented to maintain cardiac output with the expectation that harmful effects to the liver will be avoided.

The present experiments that observe portal hemodynamics during mechanical ventilation with PEEP attempt to distinguish between the direct effects of PEEP and those secondary to reduced cardiac output. An intact dog model is used and cardiac output is maintained at control levels by intravascular volume expansion with dextran 70 in saline prior to application of PEEP.

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Methods

Twelve mongrel dogs weighing between 16 kg and 21 kg were studied using general anesthesia with IV pentobarbital, 30 mg/kg. Controlled ventilation with room air was achieved using a volume respirator (Harvard Instruments, Cambridge, MA) with a tidal volume of 15 cc/kg and a rate of 12. PEEP was applied by placing a cannula from the expiratory port of the respirator 15 cm below the surface of a water-filled cylinder. Systemic arterial pressure (SAP) and the pressure in the intrathoracic vena cava (CVP) were measured from polyethylene catheters (2-mm ID) placed via peripheral cutdowns.

Abdominal instrumentation was performed through a midline laparotomy. Splenectomy was performed at the same time to minimize acute intravascular volume changes.[2] The incision was closed in one layer prior to commencing the experimental protocol. Portal vein pressure (PVP) was measured at the porta hepatus from a polyethylene catheter (1.14-mm ID, Biomedical I-Cath, Murray Hill, NJ) secured with a purse string suture. The intraluminal pressure gradient between portal vein and intrathoracic inferior vena cava (PVP-CVP) was measured directly by connecting the catheters to the two sides of a bidirectional pressure transducer. Intrapleural pressure was estimated by measuring intraesophageal (IE) pressure recorded from a nasogastric tube with an air-containing esophageal balloon (National Catheter CO., Argyle, NY). Intraabdominal (IA) pressure was measured from a similar balloon-tipped catheter placed

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adjacent to the porta hepatus above the transverse mesocolon and brought out through a stab wound in the abdominal wall. All pressures were measured using Hewlett-Packard 267-BC transducers and Hewlett-Packard recording apparatus.

Cardiac output (CO) was measured by thermodilution using the thermister tip of a flow directed pulmonary artery catheter (Kimray Med Associates, Oklahoma City, Oklahoma) and a cardiac output computer (KMA Model 3500, Oklahoma City, OK). The average of duplicate CO measurements was used. Portal vein flow (PVF) and superior mesenteric artery flow (SMAF) were measured with electromagnetic flow probes (Carolina Medical Electronics, King, NC). A 12-mm circumference probe was placed snuggly around the origin of the SMA and an 18-mm or 20-mm circumference probe was fitted around the portal vein in the porta hepatus. Flow probes were zeroed *in situ* by clamping the vessel on either side of the probe. Stability of the zero reference was checked at the conclusion of the experiments by measuring the "flow" immediately after sacrifice of the animal at which time measured flow was ±10 cc/min of zero. Hepatic resistance to portal flow was calculated in arbitrary resistance units by dividing the directly measured intraluminal pressure gradient between portal vein and inferior vena cava (mmHg) by the portal vein flow (ml/min).[5]

Blood gases were measured on freshly drawn arterial blood using conventional electrodes (Radiometer ABL II C, Acid Base Laboratory, Copenhagen). Hemoglobin concentration was measured by standard techniques. Rectal temperature was maintained at 37 ± 1 C by heating pad and electric lamps. Statistical comparison was by two-tailed Student t test, using the paired t test when comparing animals with their own control and unpaired t test for comparing different measurements performed at the same time. Data are recorded as mean ± standard error.

Experimental Protocol

Following control measurements, CO was augmented by intravascular volume expansion with dextran 70 in normal saline (Macrodex®, Pharmacia, Piscatawy, NJ). An average of 17 ± 1.2 cc/kg of dextran was administered. The colloid oncotic pressure of four samples of dextran was measured using a colloid osmometer (Wescor, Inc., Logan UT) and was found to be 44 mmHg. PEEP (15 cmH_2O) was applied after dextran administration, with the goal being that the combined effects of PEEP and intravascular volume expansion would bring CO back to control levels (*i.e.*, levels measured prior to dextran infusion). Measurements were made 15 minutes after administration of dextran, 15 minutes following application of PEEP, and, finally, 30 minutes after removal of PEEP.

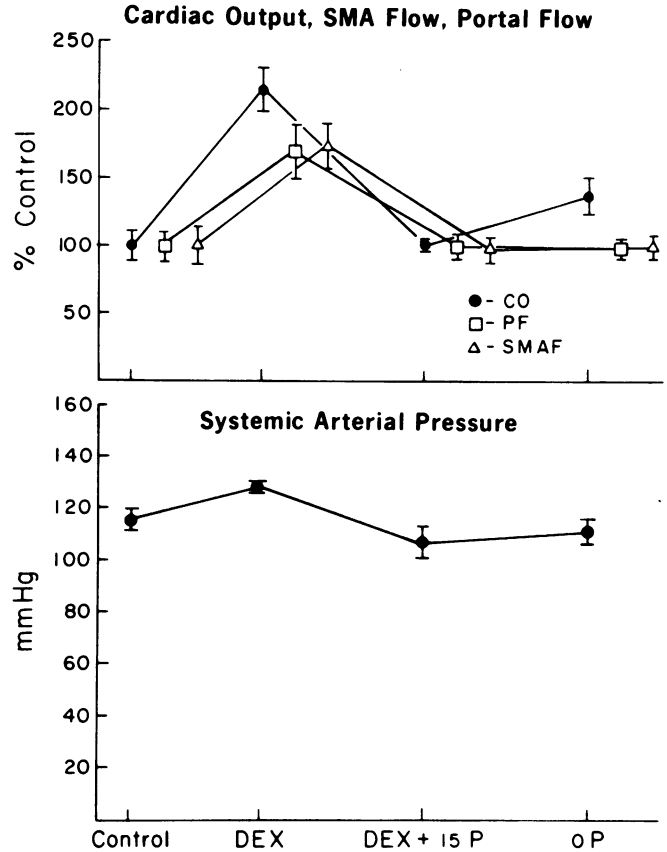

FIG. 1. Cardiac output, superior mesenteric artery flow, portal flow and mean systemic pressure. Sequence of measurements is control, after dextran infusion (DEX), after addition of 15 cmH_2O PEEP (DEX + 15 P) and finally after removal of PEEP (0 P) (n = 9).

Results

Intravascular volume expansion with dextran increased all flows in all 12 dogs. PEEP (15 cmH_2O) reduced all flows. In three dogs, CO with PEEP fell to less than 75% control ($\bar{X}$ = 66 ± 6%). In these three dogs, PF and SMAF after dextran and PEEP were each reduced to 71 ± 4% control, *i.e.*, approximately the same extent as CO was reduced. Since the experimental design was to have the combined effect of PEEP and intravascular volume expansion produce a cardiac output at control levels, these three dogs were excluded from the data analysis which looked at the course of events over time. In the remaining nine dogs, the combination of intravascular volume expansion with dextran, followed by 15 cmH_2O PEEP, resulted in the average of all flows being within 3% of control (Fig. 1). Thirty minutes after removal of PEEP, CO was moderately elevated, but both visceral flows remained at control levels.

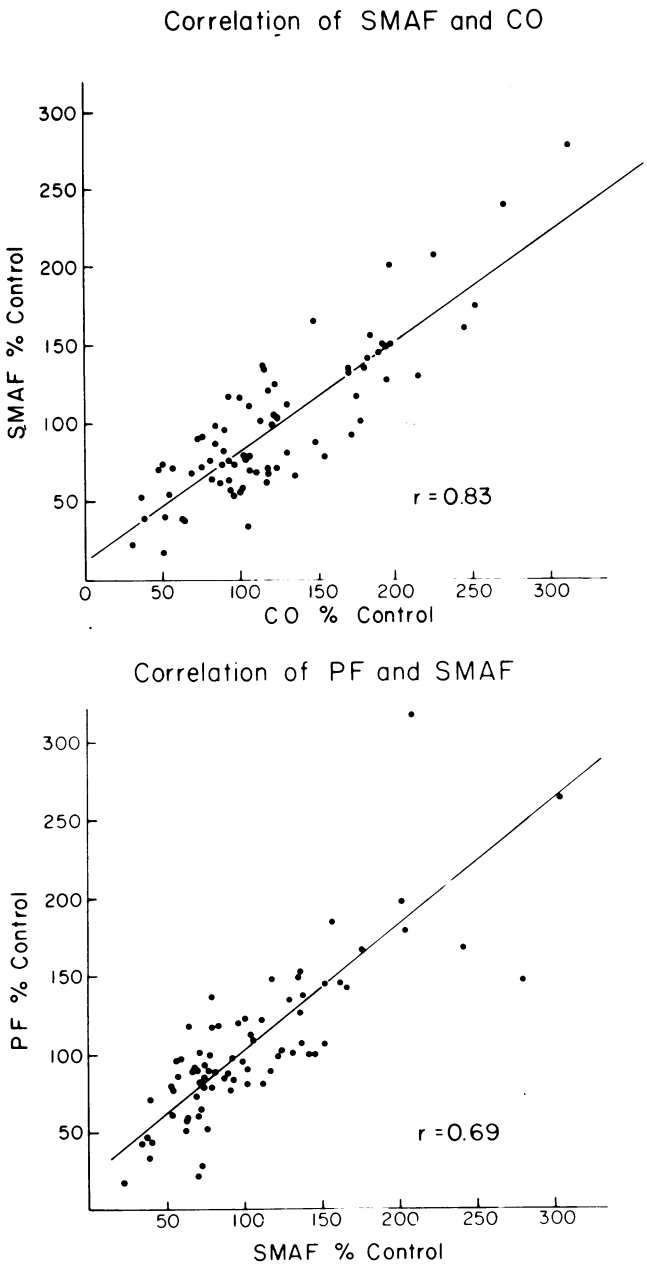

FIG. 2. Correlation of superior mesenteric artery flow with cardiac output and correlation of portal flow with superior mesenteric artery flow. Flows plotted as per cent control. Data includes all 12 dogs and all measurements after control are included.

The data from all 12 dogs were used to calculate the regression lines where the relation of two variables is displayed independent of time (Fig. 2). Figure 2 shows the linear correlation between SMAF and CO and between PF and SMAF.

Systemic arterial pressure increased with intravascular volume expansion, then fell to the control range after application of PEEP and remained stable after removal of PEEP (Fig. 1).

In Table 1, the effect of PEEP on venous pressures and intracavitary pressures is compared with the effect of intravascular volume expansion. PVP and CVP measured relative to atmosphere were increased both by PEEP and by intravascular volume expansion. PEEP, however, increased both intracavitary pressures, whereas intracavitary pressures were not affected by intravenous volume expansion. Thus, PEEP did not increase the transmural pressure in either the portal vein or the inferior vena cava, whereas the transmural pressures in both veins were increased with intravascular volume expansion. In figure 3, the directly measured intraluminal pressure gradient between portal vein and central venous pressure is displayed for the course of the entire protocol. The intraluminal pressure gradient fell with the addition of PEEP but increased with intravascular volume expansion. Figure 4 displays the course of hepatic resistance. No resistance differed significantly from control.

PaO_2 and $PaCO_2$ all remained within normal range during the course of the experiment. Dextran infusion acutely lowered hemoglobin concentration 2.6 g/dl, and the average decrease was 1.8 g/dl at the time of final measurements of PEEP.

Discussion

In previous experiments, PEEP has consistently reduced cardiac output.[1-4] The question of whether or not PEEP also redistributes cardiac output has been approached by comparing the proportionate reduction in visceral organ flow to the reduction in total cardiac output.[1-4] Newborn lambs breathing spontaneously against 15 cm H_2O expiratory pressure had a 20% reduction in CO and renal blood flow, but no change in arterial flow to the gastrointestinal tract, liver, or spleen as measured by labeled microspheres.[4] In contrast, studies with labeled microspheres in adult dogs on controlled me-

TABLE 1. *Changes in Vascular and Intracavitary Pressures with Addition of PEEP and with Expansion of Intravalvular Volume*

	PEEP	Intravascular Volume
Portal Vein	2.9 ± 0.9	2.4 ± 0.6
Intraabdominal	2.7 ± 0.3	0*
Intrathoracic cava (CVP)	4.6 ± 0.3	1.2 ± 0.3
Intrapleural	3.7 ± 0.4	0*
PVP-CVP	−1.7 ± 0.9	1.2 ± 0.5

All pressures in mmHg measured relative to atmosphere ($\bar{X}$ ± SE). Sequence of measurements is the same as is illustrated in figure 3. The PEEP column is the average difference between measurements at "dextran + PEEP" and the previous measurements with dextran alone. The intravascular volume column is the difference between measurements at "dextran" and the preceeding control measurements.

* N.S., all other differences are significant at $p < 0.05$ or $p < 0.01$.

chanical ventilation found that the addition of 15 cmH_2O PEEP reduced hepatic arterial flow to 48% of control, whereas CO was reduced to only 61% of control.[1] Hemorrhage which reduced CO to a similar level reduced hepatic arterial flow to 83% of control. The apparent disproportionate fall in hepatic arterial flow with PEEP led these authors to conclude that PEEP had a direct effect on hepatic blood flow quite apart from the secondary effect of reduced cardiac output.

In studies specifically of portal blood flow, Johnson and Hedley-Whyte found both CO and PF reduced to 77% of control by the addition of 5 to 7 cmH_2O end expiratory pressure to mechanical ventilation.[2] They also observed an increase in portal vein pressure with PEEP and concluded that the reduction in portal vein flow resulted from an increase in vascular resistance at the hepatic sinusoidal level.[2,6] This increase in hepatic resistance was thought to be a direct pressure effect on the liver and intraabdominal pressure consequent to PEEP increasing lung volume.[2] Portal vein pressure was measured relative to atmosphere and the increase was approximately 2 cmH_2O (1.5 mmHg).

Our own previous studies also noted that PEEP reduced both CO and PF by the same proportion. We, too, found that PVP measured relative to atmosphere increased with PEEP; however, measurements of intraabdominal pressure in a separate group of dogs with PEEP suggested that intraabdominal pressure also increased with PEEP[3] and, thus, there might not be a real increase in transmural portal pressure.

The problem with previous experiments[1-4] has been that cardiac output invariably fell below control level with the addition of PEEP. The present study attempted

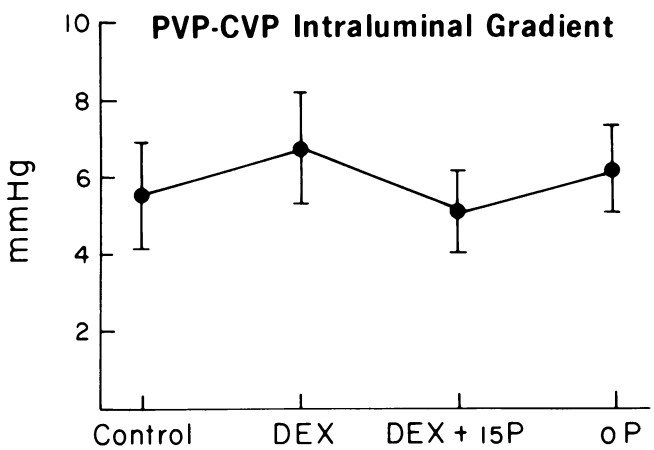

FIG. 3. Directly recorded intraluminal pressure differential between portal vein and intrathoracic vena cava (PVP-CVP). Only the initial increase in gradient with dextran differs from control ($p < 0.05$, $n = 9$).

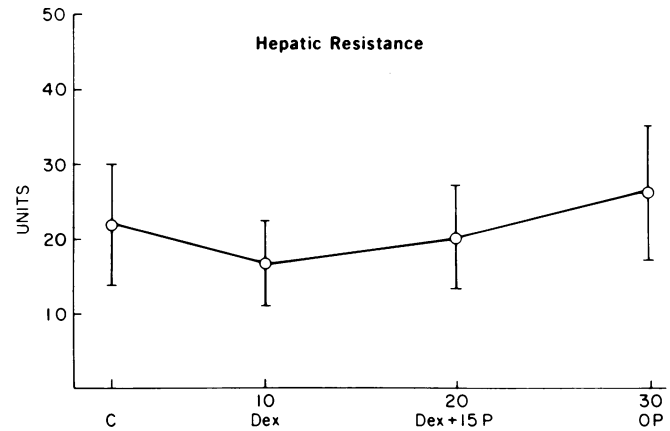

FIG. 4. Hepatic resistance to venous flow calculated as the measured intraluminal pressure gradient between portal vein and intrathoracic cava (mmHg) divided by portal flow (ml/min). No measurement differs significantly from control ($n = 9$).

to keep cardiac output at control levels in order to distinguish clearly whether the observed changes in portal hemodynamics were really the effect of increased airway pressure and lung volume or whether they were secondary to the coincident reduction in cardiac output. In nine animals, the infusion of dextran prior to PEEP resulted in cardiac output being maintained at control levels, and in these nine animals, visceral flows remained at control levels. In the three animals in which CO was reduced below control levels despite prior dextran infusion, visceral flows were reduced to the same extent. The linear relationship between SMAF and PF suggests that variation in the arterial inflow to the gut is the major determinate of venous outflow. The correlation between CO and SMAF emphasizes the central importance of cardiac output to visceral hemodynamics during ventilation with PEEP. Although we have not measured hepatic arterial flow directly, our data suggest that the reduction in CO with PEEP may be the major determinant of the reduction in hepatic arterial flow as well as SMAF.

The increase in PVP measured relative to atmosphere as well as the level of PEEP are both greater than those reported by Johnson and Hedley-Whyte. However, the present experiments demonstrate that PEEP also increases intraabdominal as well as intrapleural pressure. Thus, we have demonstrated no significant increase in transmural portal pressures with PEEP.

Direct measurement of the intraluminal pressure gradient between portal vein pressure and the intrathoracic vena cava avoids the problem of measuring transmural vascular pressures in two body cavities which have different intracavitary pressures. These confirm that there is no increase in the venous pressure gradient across the

liver with PEEP. Similarly, PEEP alone did not alter hepatic resistance to venous flow. Critical evaluation of the experiments which showed an increase in hepatic sinusoidal resistance secondary to an increase in abdominal pressure[2,6] reveals that hepatic sinusoidal resistance increased only at intraabdominal pressures ranging between 15 cmH_2O and 25 cmH_2O,[6] which are much higher than the increase in abdominal pressure that we have observed with 15 cmH_2O PEEP.

We conclude that the increases in lung volume and/or alveolar pressure with PEEP do not appear to have a direct effect on portal hemodynamics. The lung volume and pleural pressure changes with PEEP do, however, reduce cardiac output, and the portal hemodynamic changes with PEEP derive from this reduction in cardiac output. Our data show no redistribution of cardiac output away from SMA, although hepatic arterial flow was not measured specifically. These data emphasize the need for careful management of cardiac output in patients ventilated with PEEP. The hemodynamic consequences of PEEP must be considered in making clinical judgments as to when to use PEEP, how much PEEP to apply, and what mode to be used in administering PEEP. In these experiments, we have looked only at controlled ventilation. Spontaneous breathing or intermittent mandatory ventilation with PEEP may reduce the untoward effects of PEEP on blood flow since these two ventilatory modes do not increase mean intrathoracic pressure to the same extent as controlled ventilation with PEEP.

Judgment must weigh the potential benefit of PEEP on lung function and oxygen transfer against the harmful effect on cardiac output and the potential for secondary visceral organ damage. These judgments are particularly critical in patients with low cardiac output.

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